Arabian Journal of Chemistry (2016) 9, 25–31

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Rapid, efficient and solvent free microwave mediated synthesis of aldo- and ketonitrones

Loredana Maiuolo [a,*], Antonio De Nino [a,*], Pedro Merino [b], Beatrice Russo [a], Gaetano Stabile [a], Monica Nardi [a], Napoleone D'Agostino [a], Tatiana Bernardi [c]

[a] *Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, Via Bucci cubo 12 C, 87036 Rende (CS), Italy*
[b] *Laboratorio de Síntesis Asimétrica, Departamento de Síntesis y Estructura de Biomoléculas, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), Universidad de Zaragoza-CSIC, 50009 Zaragoza, Aragón, Spain*
[c] *Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Ferrara, Via Borsari 46, 44121 Ferrara, Italy*

Received 3 October 2014; accepted 31 January 2015
Available online 11 February 2015

KEYWORDS

Aldonitrones;
1,3-Dipoles;
Ketonitrones;
Microwave;
Neat reactions

Abstract A library of *C*-alkyl and *C*-aryl nitrones has been obtained by direct condensation of primary *N*-substituted hydroxylamine hydrochlorides with various aldehydes and ketones without catalysts or base. The synthetic procedure, performed under MW irradiation in the absence of solvent, does not require the presence of a base, is fast, clean, high-yielding and characterized by simple work-up.

1. Introduction

Nitrones (**1**) are useful and versatile intermediates in organic synthesis. They react as electrophiles with organometallics compounds, with indoles and pyrroles (Denis et al., 1997; Berini et al., 2008) or with various substrates (Merino, 2005) and behave as 1,3-dipoles in cycloaddition reactions (Martin and Jones, 2002; Merino, 2004, 2011; Bortolini et al., 2008). In the latter case the nitrone functionality plays an important role in the organic chemistry due to its ability to generate multiple stereocenters in a single cycloaddition step. In addition, nitrones have relevant applications in biological therapeutic studies. As an example α-phenyl-*N*-tert-butylnitrones (PBN) show neuroprotective properties (Dhainaut et al., 2000; Balogh et al., 2005; Kim et al., 2007; Villamena et al., 2012) and many derivatives obtained from 1,3-dipolar cycloaddition of nitrones with alkenes exhibit potential biological activity (Chiacchio et al., 2001; Chiacchio et al., 2003; Merino et al., 2005; Bortolini et al., 2010, 2011).

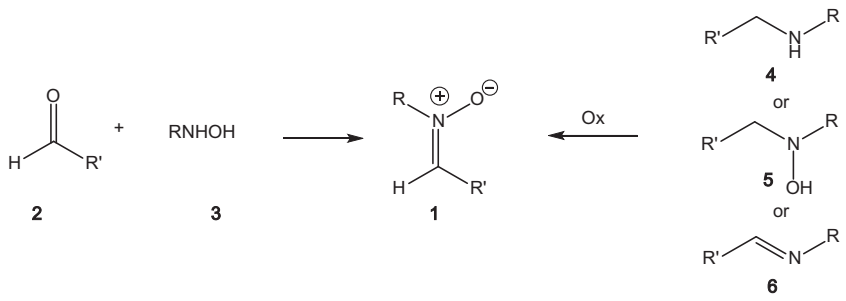
The most common procedures for the preparation of these compounds are summarized in Scheme 1 and include: (i) the condensation of carbonyl compounds **2** with *N*-substituted hydroxylamines **3** in the presence of a drying agent (Torssell and Zeuthen, 1978; Masson et al., 2002; Young and Kerr, 2003); (ii) the oxidation of secondary amines **4** or *N*,*N*-disubstituted hydroxylamines **5** by a variety of oxidants including mercury oxide, manganese(IV) oxide (Cicchi et al., 2001;

* Corresponding authors. Tel.: +39 0984492853, +39 0984492043; fax: +39 0984493307.
E-mail addresses: maiuolo@unical.it (L. Maiuolo), denino@unical.it (A. De Nino).

Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2015.01.015



Scheme 1 General methods for the synthesis of aldonitrones 1.

Guinchard et al., 2007) and hydrogen peroxide in the presence of a catalytic amount of sodium tungstate (Breuer, 1982; Cardona et al., 2008); or (iii) the catalytic oxidation of imines **6** employing either an excess of potassium permanganate under phase-transfer conditions (Christensen and Jørgensen, 1989) or a methyltrioxorhenium/UHP (Soldaini et al., 2007).

In any case there are in literatures other methods of nitrones formation such as one pot reduction–condensation of nitro compounds with aldehydes (Gautheron-Chapoulaud et al., 2001) or benzaldehyde derivatives (Choteau et al., 2012) or via Cope-type hydroamination of allenes (Moran et al., 2009). Most of these oxidation methods employ heavy metals as catalysts which can be a source of contamination for the preparation of compounds with therapeutic use. In recent years the interest has been directed toward more environmentally friendly procedures based on MW-assisted reactions (Shridharan et al., 2004; Banerji et al., 2004; Andrade et al., 2008; Reyes et al., 2010; Chavarría et al., 2012; Petkes et al., 2014), ball-mill methodologies (Colacino et al., 2008) and the use of nonconventional solvents or solvent-free conditions, with a particular emphasis on ionic liquids or water as green reaction media (Valizadeh and Shockravi, 2005; Valizadeh et al., 2009; Valizadeh, 2010). While considering the good or excellent results obtained with the methods yet described, all of them show some limitations as the long reaction times, the use of organic solvents and the employment of an excess of carbonyl compounds associated with tedious purification practices.

Here we wish to present a greener approach to this problem consisting in the direct synthesis of various nitrones by solvent-free condensation of primary aryl- or alkylhydroxylamine hydrochlorides with aromatic aldehydes and ketones under microwave irradiation. The advantages are short reaction times, high yields, clean reactions without formation of by-products and related procedures of purification, absence of metal catalysis, typical conveniences of microwave application (Lidstrom et al., 2001; Kappe, 2004; Dallinger and Kappe, 2007).

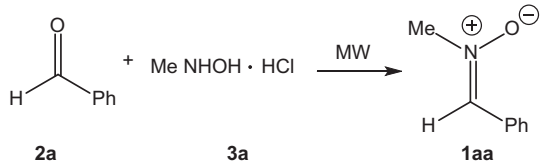
2. Results and discussion

2.1. Model reaction to synthesize the nitrone *1aa*

Initially, we selected the condensation between benzaldehyde **2a** and *N*-methylhydroxylamine hydrochloride **3a** as a model reaction by using an unmodified household microwave oven, in absence of solvent and base (Scheme 2). Preliminary results, collected in Table 1, were obtained by varying the main reaction factors *i.e.* MW power, reactants molar ratio, and reaction time.

The procedure is simple and consists of mixing the two components in a vortex, followed by transfer of the mixture in an apposite open vessel, which is placed within a household microwave oven, at 450–600 W irradiation power, for times ranging from 5 to 15 min. After the appropriate time, monitored by TLC, hot EtOAc was added to the reaction mixture, that appeared as a syrup, producing the product as a solid precipitate. The isolated product was subjected to ^{1}H, ^{13}C NMR spectroscopy and HRMS analysis, to confirm the formation of **1aa**.

As shown in Table 1, the use of MW power at 450 W (entry 1) does not lead to the complete formation of compound **1aa** for which it is necessary to apply an irradiation at 600 W (entries 2–5). Moreover, choosing the 1.5:1 ratio of the **2a**/**3a** couple (entry 3), lower yields and formation of by-products is observed. The stoichiometric ratio of aldehyde and hydroxylamine hydrochloride actually shows three advantages: (1) quantitative yields, (2) no formation of by-products and (3) the absence of work-up and lengthy purification steps. In agreement with literature reports, the stereochemical outcome of the reaction shows the highly selective formation of the more stable Z form (Hassan et al., 1998), that we confirmed by ^{1}H NMR spectra and by comparison with literature data. The model reaction was confronted with the results obtained when the compound **3a** was allowed to react with a slight excess of aldehyde **2a** (1.2 eq) and a base (1.3 eq of NaOAc) (entry 4). Although the yield was high (90%), it is possible to conclude that the use of a base is not necessary for the progress of the reaction. Moreover, when the nitrone **1aa** was formed by reaction between the aromatic aldehyde **2a** and neutral *N*-methylhydroxylamine, a yield of 53% was observed, supporting the thesis that the presence of hydroxylamine hydrochloride is necessary for the complete performance of the reaction (entry 5). This result is in agreement with the well-known requirement of acidity in several nucleophilic additions to carbonyl compounds, such as the formation of an enamine. Whereas either using directly the hydroxylamine hydrochloride or in the presence of sodium acetate (the *in situ* formed acetic acid is present in the medium), the reaction per-



Scheme 2 Model reaction to synthesize nitrones.

Table 1 Formation of *N*-methyl-*C*-phenyl nitrone **1aa**.

Entry	Aldehyde	Hydroxylamine·HCl	Hydroxylamine	Base	Molar ratio	MW (W)	Δ (°C)	Time (min)	Product	Yield (%)
1	**2a**	**3a**	–	–	1:1	450	–	15	**1aa**	52
2	**2a**	**3a**	–	–	1:1	600	–	5	**1aa**	92
3	**2a**	**3a**	–	–	1.5:1	600	–	5	**1aa**	79
4	**2a**	**3a**	–	NaOAc	1.2:1:1.3	600	–	5	**1aa**	90
5	**2a**	–	*N*-Methyl-	–	1:1	600	–	5	**1aa**	53
6	**2a**	**3a**	–	–	1:1	–	160	1440	**1aa**	12

forms well (90–92%), a lower yield (53%) is observed. In addition a further experiment was carried out by heating the reaction between aldehyde **2a** and *N*-methylhydroxylamine·HCl **3a** (entry 6) without adding of solvents; in this case it observed a very low formation of nitrone **1aa**, thus confirming for this method the importance of microwave irradiation.

*2.2. Synthesis of aldonitrones **1ab–1qc***

With these results in hands, we next explored the effect of different substituents on **2** and **3** by using different aromatic aldehydes **2a–q** and *N*-methyl (**3a**), *N*-benzyl (**3b**) and *N*-phenyl hydroxylamine hydrochloride (**3c**). The results obtained are shown in Table 2.

All reactions afforded the desired product in yields varying from very good to excellent and high purity. In almost all cases the procedure does not require particular work-up and the products can be separated simply by adding hot EtOAc and a small amount of hexane if necessary. Slightly lower yields were observed only in one case (entry 17), associated with the incomplete consumption of the reagents and with the formation of uncharacterized by-products. Consequently, flash-chromatography purification was required.

*2.3. Synthesis of ketonitrones **1ra–1ua***

Considering the general different and scarce reactivity of ketones compared to aldehydes in the nitrones formation (Exner, 1951; Pfeiffer and Beauchemin, 2009; Nakamura et al., 2014), we decided to test the method also with these substrates. The pertinent results are collected in Table 3.

As shown in Table 3, a few adjustments of the reaction conditions to the new substrates were required to minimize by-product formation. In particular, a slight excess of ketone for the formation of nitrones **1ra** and **1sa** (entries 1 and 2, Table 3) with respect to hydroxylamine was required to obtain the expected products in acceptable yields. On the contrary we observed that longer reaction times and different ratio of the reagents produced a large amount of uncharacterized by-products.

3. Experimental

Commercial starting materials were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 500 MHz and 75.5 and 125.7 MHz, respectively, in $CDCl_3$ and DMSO-d_6 using tetramethylsilane (TMS) as internal standard (Bruker ACP 300 MHz and 500 MHz). Chemical shifts are given in parts per million and coupling constants in Hertz. High resolution mass spectra (HRMS) were acquired on a Q-star pulsar-i (MDS Sciex Applied Biosystems, Toronto, Canada) equipped with an ion-spray source at 10,000 resolution. Household microwave model: Samsung GE82P, 230 V, 50 Hz. The purity was established for all products by a short range (1 °C) of melting point and by NMR spectra. Melting points were obtained on a Kofler apparatus.

*3.1. General procedure for the synthesis of aldonitrones **1aa–1qc***

The selected aldehyde (500 mg) and the hydroxylamine hydrochloride (1 eq) were placed in a Pyrex container and mixed in a vortex. The mixture was transferred to an household microwave oven and irradiated with a 600 W power. After the appropriate time hot EtOAc was added to crude oil, by adding of a few drops of hexane if necessary, isolating the pure nitrone as solid, after filtration under vacuum and washing with cold dry EtOAc. The purification of compounds **1qa–1qc** was realized by flash chromatography ($CHCl_3$/MeOH 98.75/1.25 v:v).

All nitrones were characterized by HRMS, ^{1}H and ^{13}C NMR and compared with literature data: **1aa–1ac**, **1db**, **1hb**, **1jb**, **1qb** (Palomo et al., 2005); **1ca–1cb**, **1eb**, **1gb**, **1oa** (Bortolini et al., 2011); **1da–1dc**, **1ja**, **1la**, **1na**, **1qa** (Chan et al., 1995); **1ec** (Oravec et al., 1991); **1fa** (Hassan et al., 1998); **1fc** (Valizadeh and Dinparast, 2009); **1ga**, **1gc** (Anand and Singh, 2012); **1ha**, **1ka–1kc**, **1ob** (Colacino et al., 2008); **1hc** (Herrera et al., 2001); **1ia** (Wagner and Garland, 2008); **1ib** (Lu et al., 2012); **1ic**, **1pc** (Nelson et al., 2001); **1jc**, **1lb**, **1lc**, **1hc** (Liard et al., 2003); **1ma**, **1mb** (Coşkun and Parlar, 2005); **1mc** (Frontana-Uriba and Moinet, 1999); **1nb** (Soldaini et al., 2007); **1oc** (Andrade et al., 2008); **1pa** (Camiletti et al., 1994); **1pb** (Evans et al., 2006); **1pc** (Nelson et al., 2001). The full characterization of nitrones **1ba**–**1bc**, **1cc**, **1ea**, **1fb** and **1qc** is reported. Yields were calculated on isolated compounds.

*3.1.1. (Z)-N-methyl-C-(2,6-dichlorophenyl) nitrone **1ba***

White solid, yield 93%, m.p. 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H, CH_3), 7.22–7.39 (m, 3H, Ar), 7.53 (s, 1H, =CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 53.5, 128.1, 128.3, 130.5, 130.9, 135.5. ESI-HRMS theoretical for $[C_8H_7Cl_2NO + H]^+$ 203.9977 found 203.9976.

*3.1.2. (Z)-N-benzyl-C-(2,6-dichlorophenyl) nitrone **1bb***

White solid, yield 90%, m.p. 154–155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (s, 2H, CH_2), 7.21–7.34 (m, 3H, Ar), 7.38–7.46 (m, 3H, Ar), 7.48 (s, 1H, =CH), 7.50–7.54 (m, 2H, Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 70.9, 128.4, 128.8, 129.4, 129.6, 130.0, 130.4, 131.2, 133.1, 136.0. ESI-HRMS theoretical for $[C_{14}H_{11}Cl_2NO + H]^+$ 280.0290 found 280.0272.

3.1.3. (Z)-N-phenyl-C-(2,6-dichlorophenyl) nitrone ***1bc***

Yellow solid, yield 93%, m.p. 111–112 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.45–7.65 (m, 6H, Ar), 7.85–7.95 (m, 2H, Ar), 8.63 (s, 1H, =CH); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 121.5, 128.1, 128.2, 128.8, 129.2, 130.6, 131.7, 134.6, 147.0. ESI-HRMS theoretical for $[C_{13}H_9Cl_2NO + H]^+$ 266.0134 found 266.0131.

3.1.4. (Z)-N-phenyl-C-(2-chlorophenyl) nitrone ***1cc***

Whitish solid, yield 97%, m.p. 49–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.55 (m, 6H, Ar), 7.68–7.85 (m, 2H, Ar), 8.42 (s, 1H, =CH), 9.52 (dd, J = 2.10, 7.92 Hz, 1H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 121.8, 127.2, 128.4, 129.2, 129.5, 130.2, 130.4, 131.5, 133.6, 149.5. ESI-HRMS theoretical for $[C_{13}H_{10}ClNO + H]^+$ 232.0523 found 232.0525.

3.1.5. (Z)-N-methyl-C-(2-fluorophenyl) nitrone ***1ea***

Pale yellow solid, yield 91%, m.p. 48–49 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H, CH_3), 7.08 (ddd, J = 1.59, 8.22, 10.98 Hz, 1H, Ar), 7.18–7.26 (m, 1H, Ar), 7.33–7.44 (m, 1H, Ar), 7.67 (s, 1H, =CH), 9.23 (td, J = 1.59, 7.65 Hz, 1H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.0, 114.5 (d, J = 1.20 Hz), 114.8, 124.4 (d, J = 3.01 Hz), 127.4 (d, J = 7.22 Hz), 128.6, 131.7 (d, J = 9.01 Hz), 159.9 (d, J_{CF} = 253.12 Hz). ESI-HRMS theoretical for $[C_8H_8FNO + H]^+$ 154.0663 found 154.0662.

3.1.6. (Z)-N-benzyl-C-(2-hydroxyphenyl) nitrone ***1fb***

Yellow solid, yield 90%, m.p. 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (s, 2H, CH_2Ph), 6.75–6.86 (m, 1H, Ar), 6.90–7.03 (m, 2H, Ar), 7.30–7.47 (m, 7H, Ar + OH), 7.48 (s, 1H, =CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 68.7, 116.5, 118.9, 118.9, 120.1, 129.2, 129.2, 129.4, 132.2, 134.1, 141.1, 159.7. ESI-HRMS theoretical for $[C_8H_9NO_2 + H]^+$ 152.0706 found 152.0701.

3.1.7. (Z)-N-phenyl-C-(4-cyanophenyl) nitrone ***1qc***

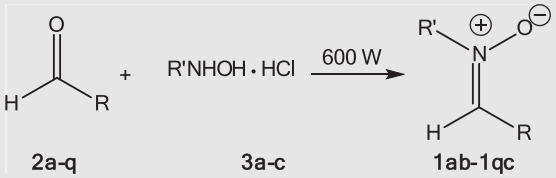
Brownish solid, yield 82%, m.p. 149–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.54 (m, 3H, Ar), 7.73–7.81 (m, 4H, Ar), 8.01 (s, 1H, =CH), 8.48 (d, J = 8.28 Hz, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 121.7, 121.7, 128.8, 129.3, 129.4, 130.6, 132.3, 132.3, 134.5, 148.9. ESI-HRMS theoretical for $[C_{14}H_{10}N_2O + H]^+$ 223.0866 found 223.0867.

3.2. General procedure for the synthesis of ketonitrones ***1ra-1ua***

The selected ketone (1.2 eq for **7r** and **7s**; 1 eq for **7t** and **7u**) and methylhydroxylamine hydrochloride **3a** (500 mg) were placed in a Pyrex container and mixed in a vortex. The mixture was transferred to an household microwave oven and irradiated with a 600 W power. The crude residue thus obtained was purified by flash chromatography ($CHCl_3$/MeOH 97.5/2.5 v:v).

Nitrones **1ra–1ua** were characterized by HRMS, ^{1}H and ^{13}C NMR and compared with literature data: **1ra**, **1sa** (Cummins and Coates, 1983); **1ta** (Clack et al., 1981); **1ua** (Vasilevskis et al., 1970).

Table 2 Synthesis of nitrones from various aldehydes and *N*-substituted hydroxylamines hydrochlorides.



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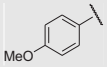
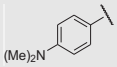
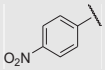
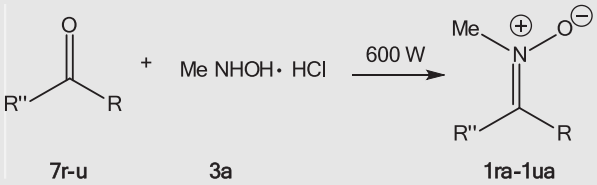
Entry	R	R′	Time (min)	Yield (%)	Product
1		Benzyl	4	94	**1ab**
		Phenyl	5	93	**1ac**
2		Methyl	5	93	**1ba**
		Benzyl	6	90	**1bb**
		Phenyl	3	93	**1bc**
3		Methyl	12	92	**1ca**
		Benzyl	15	95	**1cb**
		Phenyl	8	97	**1cc**
4		Methyl	10	90	**1da**
		Benzyl	15	95	**1db**
		Phenyl	10	96	**1dc**
5		Methyl	10	91	**1ea**
		Benzyl	15	93	**1eb**
		Phenyl	8	95	**1ec**
6		Methyl	10	90	**1fa**
		Benzyl	15	90	**1fb**
		Phenyl	8	95	**1fc**
7		Methyl	12	90	**1ga**
		Benzyl	15	92	**1gb**
		Phenyl	10	94	**1gc**
8		Methyl	4	91	**1ha**
		Benzyl	5	90	**1hb**
		Phenyl	3	93	**1hc**
9		Methyl	5	90	**1ia**
		Benzyl	4	91	**1ib**
		Phenyl	4	90	**1ic**
10		Methyl	3	91	**1ja**
		Benzyl	4	93	**1jb**
		Phenyl	5	92	**1jc**
11		Methyl	4	93	**1ka**
		Benzyl	3	98	**1kb**
		Phenyl	2	95	**1kc**
12		Methyl	4	92	**1la**
		Benzyl	4	94	**1lb**
		Phenyl	3	96	**1lc**
13		Methyl	4	90	**1ma**
		Benzyl	3	93	**1mb**
		Phenyl	3	95	**1mc**
14		Methyl	6	90	**1na**
		Benzyl	5	93	**1nb**
		Phenyl	5	96	**1nc**
15		Methyl	4	91	**1oa**
		Benzyl	3	96	**1ob**
		Phenyl	2	98	**1oc**
16		Methyl	5	92	**1pa**
		Benzyl	4	90	**1pb**
		Phenyl	3	95	**1pc**
17		Methyl	25	80	**1qa**
		Benzyl	25	83	**1qb**
		Phenyl	25	82	**1qc**

Table 3 Synthesis of nitrones **1ra–1ua** from ketones **7r–u** and *N*-methylhydroxylamine **3a**.



Entry	Ketone	Ratio ketone/hydroxylamine	Time (min)	Yield (%)	Product
1	 **7r**	1.2:1	2	40	**1ra**
2	 **7s**	1.2:1	2	43	**1sa**
3	PhCH = CHCOPh **7t**	1:1	6	60	**1ta**
4	PhCOPh **7u**	1:1	5	62	**1ua**

4. Conclusion

In summary, we have developed an economical, environmentally benign and fast method for the synthesis of a significant number of nitrones **1** by using readily available reagents without catalysts or base. The procedure involves the use of an unmodified household microwave oven, solvent-free conditions and a fast purification step. Moreover, considering the wide use of the nitrones as starting material in various reactions, this method provides high yields, short reaction time and fast procedures of purification also in the scale-up step, producing from hundreds of milligrams to some grams of nitrones without any problem of reaction times and yields. Therefore, this system can be considered as an improved alternative to other reported procedures.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2015.01.015.

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